

Submucosal Gastric Cancer With Lymph Node Metastasis

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Background and Objectives: The intraoperative assessment of lymph node metastasis of gastric cancer remains difficult and the characteristics of recurrence after gastrectomy are not well known regarding submucosal cancer.

Methods: We examined 452 patients with submucosal gastric cancer and compared the clinicopathologic features as well as recurrence patterns between the 71 cases with lymph node metastasis (group I) and the 381 without it (group II).

Results: The mean tumor sizes were 44.8 and 33.5 mm, respectively ($P < 0.01$). The incidences of lymphatic invasion and vascular invasion were 91.5% (65/71) and 45.1% (32/71) in group I, which were significantly higher than those in group II (36.7 and 14.2%, 140/381 and 54/381, respectively, $P < 0.01$). A total of 21 patients (4.6%, 21/452) experienced recurrence after undergoing a gastrectomy and hematogenic recurrence was the most frequent type of recurrence (2.0%, 9/452). However, in group I, lymphatic recurrence was most frequently observed (7.0%, 5/71), and it was more frequent than in group II (0.3%, 1/381, $P < 0.01$). The median intervals between gastrectomy and recurrence were 34.5 and 64.0 months in groups I and II, respectively ($P < 0.05$).

Conclusions: The submucosal cancer with larger size, lymphatic invasion, and vascular invasion has high risks for lymph node metastasis. Furthermore, a strict follow-up for lymphatic as well as hematogenic recurrence is important for the patients with node positive submucosal cancer, especially within 5 years after operation.

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INTRODUCTION

The incidence of early gastric cancer has increased because of the establishment of a mass screening system as well as due to advances in technical development regarding both radiological examinations and gastrofiberscopy [1]. Owing to such an increase in the number of early gastric cancer cases, the treatment options, including endoscopic therapy, laparoscopic gastric resection, and limited surgery, are now receiving a great deal of attention [2–4]. Among the various types of early gastric

cancer cases, submucosal cancer has been reported to be closely related to lymphatic or vascular invasion, lymph node metastasis, and a poor prognosis when compared with mucosal cancer. Especially submucosal gastric cancer with lymph node metastasis often leads to postoperative recurrence and a diminished survival [5–8]. For such

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cases, a gastrectomy with extended radical lymphadenectomy is the treatment of choice and limited surgery or endoscopic therapy must be avoided. However, the intraoperative assessment of the presence of lymph node metastasis remains very difficult [9] and surgeons are sometimes perplexed when trying to determine the optimal treatment strategy. It is thus important to clarify the clinicopathologic characteristics of submucosal gastric cancer with lymph node metastasis.

In terms of recurrence after gastrectomy for early gastric cancer, hematogenic recurrence is reported to be the most common [10–12]. However, the characteristics of recurrence are still not well known, especially for submucosal cancer with lymph node metastasis, the biologic behavior of which is considered to be close to that of advanced gastric cancer. For the early detection and effective treatment of recurrent disease, it is therefore important to fully understand these characteristics.

In an attempt to identify the findings correlated to lymph node metastasis and the characteristics of recurrence of submucosal gastric cancer, we histologically reviewed surgically resected specimens and examined the recurrence patterns, while paying close attention to the presence of lymph node metastasis.

MATERIALS AND METHODS

From 1972 to 1994, 2,770 Japanese patients with gastric cancer underwent gastrectomy in the Department of Gastroenterological Surgery, National Kyushu Cancer Center. Of these 2,770, 452 patients were proven to have submucosal gastric cancer by a postoperative histologic examination. All patients underwent a gastrectomy with sufficient lymph node dissection at either the D2 or D3 level in accordance with the General Rules for the Gastric Cancer Study from the Japanese Research Society for Gastric Cancer [13]. Not only group 1 nodes (regional perigastric nodes in the lesser and greater omentum) but also group 2 nodes (those along the left gastric, common hepatic, celiac, and splenic arteries) were dissected in all cases. In some cases, additional dissections were performed for group 3 nodes (nodes such as retropancreatic and hepatoduodenal nodes and those along superior mesenteric vein).

The resected stomachs were opened along the greater or lesser curvature, pinned on a wooden plate, and fixed in 10% formalin. The tumors surrounded by normal gastric tissue were cut parallel to the lesser curvature into multiple slices at 4–5 mm intervals, and then were embedded in paraffin. From each paraffin block, 5-mm thick sections were prepared and stained with hematoxylin and eosin. All 452 carcinomas were histologically reviewed with regard to the histologic type, depth of invasion, lymphatic and vascular invasion, and lymph node metastasis. The depth of invasion was determined

using microscopic sections comprising the deepest portions of penetration by tumor cells. The clinicopathologic factors were determined in accordance with the General Rules for the Gastric Cancer Study from the Japanese Research Society for Gastric Cancer [13]. The 452 patients were thus divided into two groups: Group I included 71 cases with histologically positive lymph node metastasis and group II included 381 cases without any lymph node metastasis. The clinicopathological findings, recurrence pattern, and the prognosis were compared between the two groups.

After being discharged from the hospital, the patients were entered into a regular follow-up program with physical and blood examinations and with either a barium meal study every 4 weeks, gastrointestinal fiberoscopy, computed tomography, ultrasonography, or a combination of these modalities every 6 months for the first year and thereafter at intervals of 6 to 12 months. All patients were followed for at least 5 years after operation, and the causes of death were investigated.

The mode of recurrence was classified into four patterns: hematogenic, lymphatic, local recurrence, and peritoneal dissemination. Hematogenic recurrence was defined as that occurring in organs other than the lymph node, remnant stomach, and anastomotic site, such as the liver, lung, and bone. However, lymphangitis carcinomatosa of the lung was also included in lymphatic recurrence. Local recurrence was defined as that occurring in the remnant stomach and anastomotic site.

A statistical analysis was made using Student's *t*-test, the chi-square test, Fisher's exact test, and the Mann-Whitney test. Survival curves were drawn by the Kaplan-Meier method while the generalized Wilcoxon test was used to judge the statistical significance between the two curves. Any deaths other than a recurrence of gastric cancer were censored in the statistical analysis. *P* values were all based on two-tailed tests and a difference of *P* < 0.05 was regarded as significant.

RESULTS

Clinical Factors

The clinical factors of submucosal gastric cancers are shown in Table I. The incidence of females was 52.1% (37/71) in group I (positive node metastasis group), while it was only 30.7% (117/381) in group II (negative node metastasis group). There was no statistically significant difference between either group regarding such factors as age, family history of gastric cancer, past history concerning other cancers, and the method of gastrectomy.

Pathological Findings

The pathological findings of the submucosal gastric cancers are shown in Table II. The mean size of the

TABLE I. Clinical Factors of Submucosal Gastric Cancer

Clinical factors	Number of cases (%)		<i>P</i> value
	Group I (n = 71)	Group II (n = 381)	
Age (years)	58.4	60.5	N.S. ^a
Sex			
Male	34 (47.9)	264 (69.3)	<0.01
Female	37 (52.1)	117 (30.7)	
Family history of gastric cancer			
Negative	53 (74.6)	304 (79.8)	N.S.
Positive	18 (25.4)	77 (20.2)	
Double cancer			
Negative	63 (88.7)	344 (90.3)	N.S.
Positive	8 (11.3)	37 (9.7)	
Tumor location			
Cardia	6 (8.5)	47 (12.3)	N.S.
Gastric body	21 (29.6)	147 (38.6)	
Antrum	44 (62.0)	187 (49.1)	
Gastrectomy			
Partial	62 (87.3)	339 (89.0)	N.S.
Total	9 (12.7)	42 (11.0)	

^aN.S.: Not significant.

tumors was 44.8 mm in group I, which was significantly larger than that of group II (33.5 mm, $P < 0.01$). There was no statistical difference in the macroscopic type and histological types between the two groups. Both the incidence of lymphatic invasion and that of vascular invasion were significantly higher in the cases with node metastasis than in those without metastasis ($P < 0.01$). They were recognized in 91.5% (65/71) and 45.1% (32/71) of group I, while they were observed in only 36.7% (140/381) and 14.2% (54/381) of group II, respectively. Synchronous metastasis to the liver was found in one case of group I and it was surgically resected at the time of gastrectomy.

Postoperative Recurrence. The recurrence pattern and the site after gastrectomy are shown in Table III. Of the 452 patients with submucosal cancer, 21 patients (4.6%) had recurrence. Hematogenic recurrence was the most frequently observed type (2.0%, 9/452), followed by lymphatic recurrence, local recurrence, and peritoneal dissemination with incidences of 1.3, 0.9, and 0.4% (6/452, 4/452, and 2/452), respectively. The incidence of recurrence was significantly ($P < 0.01$) higher in group I (11.3%, 8/71) than in group II (3.4%, 13/381). There was no difference in the incidence of hematogenic recurrence between both groups. On the other hand, lymphatic recurrence was most frequent (7.0%, 5/71) in group I, and the incidence was significantly higher than that in group II (0.3%, 1/381, $P < 0.01$). One of the patients with lymphatic recurrence in group I had lymphangitis carcinomatosa of the bilateral lung.

The time of recurrence is shown in Figure 1. The median interval between gastrectomy and recurrence in group I was 34.5 months, which was significantly shorter

TABLE II. Pathological Findings of Submucosal Gastric Cancer

Pathological findings	Number of cases (%)		<i>P</i> value
	Group I (n = 71)	Group II (n = 381)	
Diameter of tumor (mm)	44.8	33.5	<0.01
Macroscopic type			
Elevated	20 (28.2)	94 (24.7)	N.S. ^a
Depressed	47 (66.2)	274 (71.9)	
Flat	1 (1.4)	3 (0.8)	
Mixed	3 (4.2)	10 (2.6)	
Histological type			
Differentiated	45 (63.4)	279 (73.2)	N.S.
Undifferentiated	26 (36.6)	102 (26.8)	
Lymphatic invasion			
Negative	6 (8.5)	241 (63.3)	<0.01
Positive	65 (91.5)	140 (36.7)	
Venous invasion			
Negative	39 (54.9)	327 (85.8)	<0.01
Positive	32 (45.1)	54 (14.2)	
Liver metastasis			
Negative	70 (98.6)	381 (100)	N.S.
Positive	1 (1.4)	0	

^aN.S.: Not significant.

than that in group II (64.0 months, $P < 0.05$). However, even in group I, there was one patient who experienced recurrence in the intraabdominal lymph nodes 11 years after undergoing a gastrectomy. No remarkable relationship was recognized between the recurrence pattern and time.

Prognosis

The prognosis after gastrectomy was significantly poorer in group I than in group II ($P < 0.001$). The 5- and 10-year survival rates were 91.1 and 86.9% in group I, while they were 98.9 and 94.1% in group II, respectively (Fig. 2).

DISCUSSION

The incidence of nodal metastasis is as low as 3–5% for mucosal cancer, while it is 15–20% for submucosal cancer [5–8]. In this study examining submucosal cancer, the incidence was 15.7% (71/452), which is consistent with the findings of other reports. The higher frequency of lymph node metastasis of submucosal cancer, as compared with mucosal cancer, can be anatomically explained as follows: The submucosal layer of the gastric wall is rich in lymph vessels, while, in the mucosal layer, it is present only in the deep levels adjacent to and within the muscularis mucosae while the upper and middle levels of the gastric mucosa contain no lymph capillaries [14]. Therefore, it is important to accurately diagnose tumor invasion. Preoperative ultrasonography as well as a barium meal study and gastrofiberscopy are reported to be useful methods [15].

TABLE III. Recurrence Pattern and Site After a Gastrectomy for Submucosal Cancer

Recurrence pattern and site	Number of cases (%)		
	Group I (n = 71)	Group II (n = 381)	Total (n = 452)
Hematogenic recurrence ^a	2 (2.8)	7 (1.8)	9 (2.0)
Liver	1 (1.4)	6 (1.6)	7 (1.5)
Lung	1 (1.4)	2 (0.5)	3 (0.7)
Bone	1 (1.4)	2 (0.5)	3 (0.7)
Lymphatic recurrence	5 (7.0)*	1 (0.3)*	6 (1.3)
Local recurrence	0	4 (1.0)	4 (0.9)
Peritoneal dissemination	1 (1.4)	1 (0.3)	2 (0.4)
Total	8 (11.3)**	13 (3.4)**	21 (4.6)

*** $P < 0.01$.

^aOne patient in group I and three patients in group II had hematogenic recurrence in two different organs. Group I: One case experienced both lung and bone recurrence. The other case had liver recurrence alone. Group II: Three cases experienced recurrence in two organs (one case, both liver and bone; one case, both liver and lung; one case, lung and bone). The other four cases had liver recurrence alone.

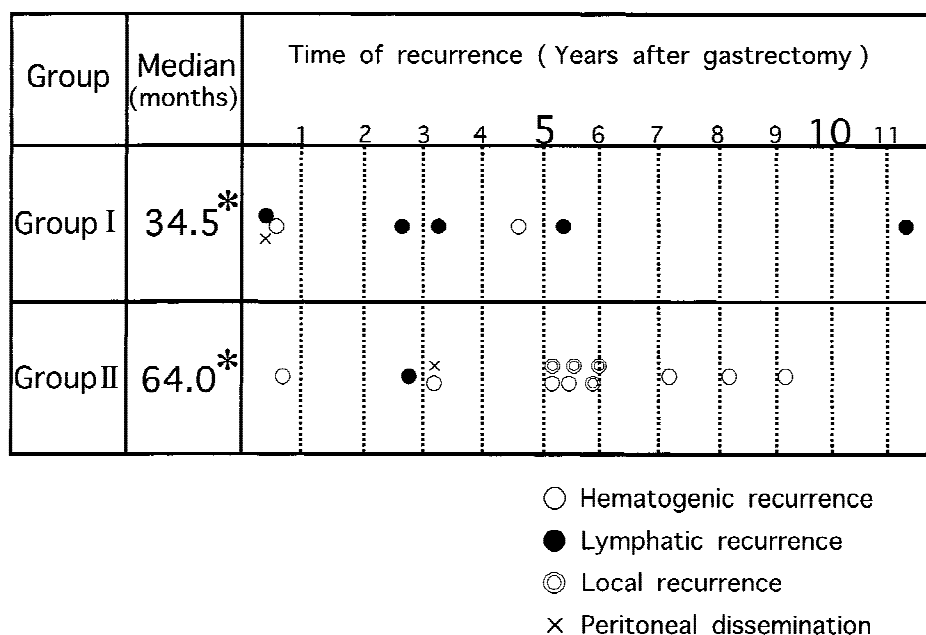


Fig. 1. The time of recurrence in patients with submucosal gastric cancer associated with lymph node metastasis (Group I) and without it (Group II). Each dot indicates the initial detection of recurrence. * $P < 0.05$ based on the Mann-Whitney test.

On the other hand, a preoperative radiological diagnosis or intraoperative macroscopic evaluation of lymph node metastasis is sometimes difficult because the metastasized node is not always enlarged. Okamura et al. [9] reported a very low accuracy in the intraoperative judgment of nodal metastasis with an accuracy rate of only about 15% for lymph nodes smaller than 15 mm in diameter. It appears to be especially difficult to intraoperatively find scattered cancer cells located in only the marginal sinus of the lymph nodes in cases of the undifferentiated type of early gastric cancer. It is therefore important to clarify the clinicopathological characteris-

tics related to lymph node metastasis. Using a multivariate analysis, Maehara et al. [16] reported that the factors related to lymph node metastasis in early gastric cancer were tumor invasion to the submucosa, lymphatic invasion, and a large tumor size. In the current study, we evaluated the clinicopathological factors in more detail regarding submucosal cancer. As a result, such factors as sex (female), tumor size, and lymphatic and venous invasion were all found to be closely related to lymph node metastasis. Among these factors, the higher incidence of females in the positive metastasis group may be due to some biological differences between the tumors occur-

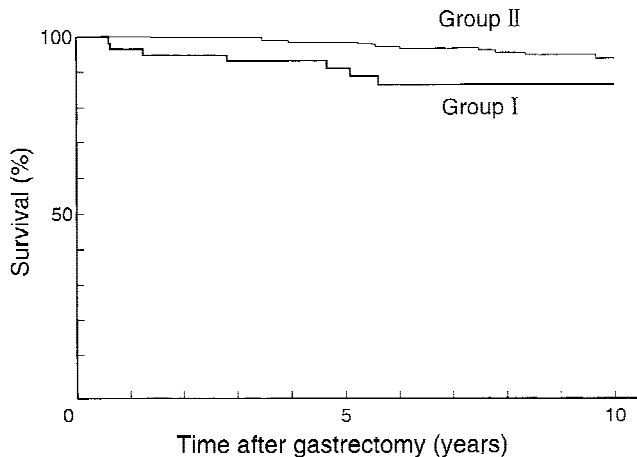


Fig. 2. Prognosis after a gastrectomy in patients with submucosal gastric cancer associated with lymph node metastasis (Group I) and without it (Group II). A statistically significant difference was observed between groups I and II ($P < 0.001$).

ring in males and females; however, these findings remain controversial. In terms of tumor size, Okamura et al. [9] also pointed out that early cancers measuring less than 2 cm in size showed a significantly lower incidence of lymph node metastasis. Regarding lymph vessel invasion, the incidence was 37% (140/381) even in patients without node metastasis, while it was extremely high (92%, 65/71) in cases with node metastasis. These results thus suggest that lymphatic invasion does not always indicate an association with lymph node metastasis; however, the existence of lymphatic invasion does indicate a high risk for lymph node metastasis. In the same manner, venous invasion is also a risk factor of lymph node metastasis in submucosal cancer. These factors are supported by the concept of the lymphatovenous channel which showed a connection between the lymphatic and blood systems [17].

For the treatment of early gastric cancer, less invasive treatments such as endoscopic mucosal resection and laparoscopic surgery have become popular due to the development of new devices and improved techniques [2–4]. Thus such treatments are now indicated for mucosal cancer. In terms of submucosal cancer, a gastrectomy with a radical lymphadenectomy (D2/D3) has now become an effective standard therapy because of the high incidence of lymph node metastasis [5,18]. In fact, limited treatments using laparoscopy or endoscopy have also been performed in some cases with submucosal cancer as well as mucosal cancer [2,3]. Our results thus suggest that an additional gastrectomy with D2/D3 lymphadenectomy should be considered when limited treatment is performed for submucosal cancer and a histological examination using the resected specimen shows either positive lymphatic or venous invasion especially in cases with tumors larger than 4 cm.

Regarding the postoperative recurrence of early gastric cancer, Ichiyoshi et al. [10] reported hematogenic recurrence to be the most common (1.8%) followed by local recurrence and lymphatic recurrence (1.0 and 0.6%, respectively). In the current study examining submucosal cancer, hematogenic recurrence was also the most common type in patients without lymph node metastasis. On the other hand, especially in the positive lymph node metastasis group, lymphatic recurrence was the most common type even through a radical lymphadenectomy (D2/D3) had been routinely indicated. The importance of a lymphadenectomy is emphasized in Japan [1,5,18], while it still remains controversial in both the United States [19] and European countries [20]. In the current study, metastasis to the extraperigastric lymph nodes (n2 or n3) was histologically recognized in 28 patients and this incidence was consistent with both the 6.2% (28/452) of total submucosal cancer cases and the 39.4% (28/71) in the positive lymph node metastasis group. We therefore believe that the results of our study do not neglect the usefulness of a radical lymphadenectomy for submucosal cancer.

Postoperative systemic chemotherapy has been applied for gastric cancer. We reported that postoperative adjuvant chemotherapy inhibited the early recurrence of early gastric cancer [21]. A recent European randomized study revealed that adjuvant systemic chemotherapy after gastrectomy improved the prognosis of node positive gastric cancer while it also effectively prevented early recurrence [22]. Chemotherapy may thus be useful for improving the prognosis of patients with node positive submucosal cancer.

In the positive node metastasis group, the cancer was more advanced at the time of operation than the negative group. It is therefore reasonable that recurrence was recognized earlier in the positive group. However, late recurrence was also observed even in the positive group. Treating a recurrence of gastric cancer is generally difficult. The early detection of recurrence is thus expected to increase the effectiveness of the therapy. Therefore, a strict follow-up for lymphatic as well as hematogenic recurrence is important especially within the first 5 years after the operation in cases with submucosal cancer associated with lymph node metastasis. However, a careful follow-up should continue for at least 10 years after surgery.

CONCLUSIONS

Large submucosal gastric cancers with lymphatic invasion and vascular invasion have high risks for lymph node metastasis. Furthermore, a strict follow-up for lymphatic as well as hematogenic recurrence is thus important for the patients with node positive submucosal cancer.

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